REMARKS

Reconsideration of this patent application is respectfully requested in view of the foregoing amendments, and the following remarks.

It is noted that claims 5 to 7, 15, 18, and 23 have been withdrawn from further consideration.

Claims 2-4, 8-14, 16-17, 19, and 27 were rejected under 35 USC § 112, 2nd paragraph as being indefinite for use of the term "of non-embryonic origin". The applicant agrees with respect to the examiner's observation that all cells would technically be of 'embryonic origin'.

Claim 27 was amended to clarify that the donor cells supplied to the morula or blastocyst have varying degrees of differentiation and are not isolated from an embryo or pre-embryo. Literal support for this amendment is provided in the specification at [0015] of the application publication 2006/0110375.

Claim 3 was amended to more clearly express that the steps of cultivating and supplying include additional sub-steps. Specifically, (a) the step of cultivating further includes a step of preparing the cells of the morula or the internal cell mass of the blastocyst in a culture dish or preparing a soluble matrix fraction from the cells, and (b) the step of supplying further includes a step of placing the donor cells to the culture dish or soluble matrix fraction. Literal support for this amendment is provided in the specification at [0022] of the application publication 2006/0110375.

Based on the above amendments and arguments, the applicant believes that the rejection of claims 2-4, 8-14, 16-17, 19, and 27 under 35 USC § 112, 2nd paragraph has been overcome, and should be withdrawn.

Claims 2-4, 8-14, 16-17, 19, and 27 were rejected under 35 USC § 103 as being obvious over *Geiger et al (Cell, 1998)* in view of *Tsukamoto et al (U.S. Pat. No. 5,914,108)* and *Eggan et al (U.S. Pat. App. No. 2002/0062493)*. The applicant respectfully traverses this rejection for the following reasons.

(a) First, it is pointed out that amended claim 27 expressly requires that the donor cells are human donor cells, which is

neither taught nor suggested in the cited art. Indeed, it should be appreciated that *Geiger et al* expressly teach against use of human donor cells for injection into blastocysts as can be taken from page 1061, right column, lines 35-43. Here *Geiger* clearly notes that histoincompatibility between allogenic donor cells and the recipient blastocyst leads to low and decreasing donor contribution, and that histoincompatibility is a limiting factor. Such report certainly fails to provide any motivation and reasonable expectation of success to use human donor cells in porcine blastocysts.

(b) Second, the Examiner appears to argue that "...*Geiger et al*. isolated human HSCs from bone marrow..."(page 7, current Office Action, line 1, emphasis added). It is entirely unclear to the applicant where in *Geiger* human bone marrow was aspirated. All *Geiger* teaches is use of murine bone marrow as is unambiguously described in the passage referred to by the examiner. Moreover, and as already pointed out above, *Geiger* considers histoincompatibility a limiting factor, and as such would not have used human bone marrow for isolation of HSCs.

(c) Third, while the applicant agrees with the Examiner's observation that *Geiger* fails to teach use of HSCs from cord blood, the applicant respectfully disagrees with the Examiner's assertion that "...it would have been obvious...to alternatively utilize HSCs from cord blood... for the predictable result of

obtaining identical HSCs for injection into the blastocysts..." (sentence spanning pages 7-8, emphasis added). It is entirely unclear to the applicant how such reasoning is supported. Among numerous other reasons, it is noted that cord blood has a distinct population and distribution of stem cells and progenitor cells as compared to bone marrow, which is developmentally more mature, embedded in an entirely different matrix, and subject to substantially lower oxygen partial pressure. Should the Office Action insist on the position that it would be predictable to obtain identical HSCs from bone marrow and cord blood, the applicant respectfully requests a citation and quote in support thereof.

(d) Fourth, the Examiner properly recognized that the murine blastocysts of *Geiger* would not have a reduced or restricted survivability. However, the applicant respectfully disagrees with the Examiner's argument that "...selection of blastocysts with reduced or restricted survivability ...would have been obvious...[because such blastocysts]...have ICMs having reduced survivability...[and thus]...would reduce competition between endogenous stem cells and implanted stem cell for stem cell niches during development...." (page 8, lines 7-11, emphasis added).

In referring back to *Geiger* with regard to the reduced competition, it is noted that the Examiner cites *Geiger* out of

context. Properly read, it is emphasized that *Geiger* discusses the take-rate of donor cells and observed that the critical parameter for donor contribution is the blastocyst age (page 1061, right column, lines 19-24). Indeed, if anything, *Geiger* suggests that donor cell injection must be early, rather than later.

Moreover, *Geiger* expressly refers to alternatives in which the donor contribution could be increased (page 1061, right column, lines 32-34) where blastocyst c-kit mutants are presented as a suitable and promising route. It should be appreciated that *Geiger* at the time of publication had the knowledge of *Eggan (U.S. Pat. App. No. 2002/0062493)* available but failed to present such teaching as alternative. Once more, early implantation and improvements of recipient cells was deemed suitable, but not reduction or restriction of survivability as proposed by the Office Action.

(e) Fifth, it should be recognized that the Examiner's argument of use of blastocysts with reduced or restricted survivability for reasons of reduced competition between endogenous stem cells and implanted stem cell for stem cell niches during development is specious, especially in light of later comments by *Geiger*. In order to provide any competitive benefit to the implanted stem cells as proposed by the Office Action, the endogenous stem cells (ICMs) must have reduced or

restricted survivability, which necessitates that the entire blastocysts prior to implantation has a reduced or restricted survivability. Such scenario, however, leads to expansion of the injected stem cells over the host cells, which will "...most probably affect the development and growth of the injected blastocyst..." (page 1062, lines 1-4). Clearly, such expectation by *Geiger* fails to provide any motivation for the reduced or restricted survivability of the blastocyst as argued by the Examiner.

(f) With respect to *Eggan* it is noted that the Examiner's assertion regarding the cells of the developing embryo is incorrect. More specifically, the Examiner stated that "...donor cells injected into the tetraploid blastocyst are ultimately without competition, and the donor cells will give rise to all cells of the developing embryo..." (page 8, lines 16-18, emphasis added). While the Examiner referred to *Eggan* in support of this statement, no specific page and line number was provided. A close review of *Eggan* reveals that the Examiner's argument is factually incorrect. On the contrary, *Eggan* expressly describes in [0043-0045] genetic heterogeneity, which can only be observed where the embryo is a chimeric embryo. Thus the Office Action argument of embryos consisting exclusively of the donor cells is untenable.

(g) Finally, it should be appreciated that the teaching of *Geiger* as a whole emphasizes that "...developmental stage of the hematopoietic microenvironment controls the developmental fate of transplanted progenitor cells..." (abstract, last sentence). As such, a reduction or restriction of survivability of the host blastocyst is certainly not suggested. Thus, *Geiger* also fails to provide a reasonable expectation of success.

The deficiencies in the teachings of the primary reference *Geiger* are not overcome by the secondary reference to *Tsukamoto U.S. Patent No. 5,914,108*.

Consequently, in view of the amendments and arguments provided above, the applicant believes that the rejection of claims 2-4, 8-14, 16-17, 19, and 27 under 35 USC § 103 should be withdrawn.

In view of the present amendments and arguments, the applicant believes that all claims are now in condition for allowance. Therefore, the applicant respectfully requests that a

timely Notice of Allowance be issued in this case.

Respectfully submitted,
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Enclosure: Petition Three Month Extension of Time (Small Entity)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: COMMISSIONER OF PATENTS, Alexandria, VA 22313-1450 on June 10, 2009.

Amy Klein

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